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Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes

Short title: Pregnancy glycemic targets in type 1 diabetes

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Abstract

Objective To assess the relationship between second and third trimester glycemic control and adverse outcomes in pregnant women with type 1 diabetes, as uncertainty exists about optimum glycemic targets.

Research Design and Methods Pregnancy outcomes were assessed prospectively in 725 women with Type 1 diabetes from the Diabetes and Pre-eclampsia Intervention Trial. A composite adverse outcome of perinatal death, shoulder dystocia, nerve palsy, fracture and neonatal intensive care was included. HbA1c (A1C) values at 26 and 34 weeks' gestation were categorised into 5 groups; the lowest, <6.0% (42mmol/mol), being the reference. Average pre- and post-prandial results from an eight-point capillary glucose profile the previous day were categorised into 5 groups; the lowest (pre-prandial <5.0mmol/l, post-prandial <6.0mmol/l) being the reference.

Results An A1C of 6.5-6.9% (48- 52mmol/mol) at 26 weeks' gestation was associated with a significantly increased risk of: pre-term delivery (odds ratio 2.5 [95% CI 1.3-4.8]), pre-eclampsia (4.3 [1.7-10.8]), large for gestational age (LGA) (2.4 [1.4-4.5]), need for a neonatal glucose infusion (2.9 [1.5-5.6]) and a composite adverse outcome (3.2 [1.3-8.0]). The risks increased with increasing A1C with no thresholds. Results were similar at 34 weeks' gestation. Glucose data showed less consistent trends, although LGA was associated with higher pre- and post-prandial glycemia, and the risk of composite adverse outcome increased with pre-prandial glucose levels between 6.0-6.9mmol/l at 34 weeks (3.3[1.3-8.0]).

Conclusions A1C≥ 6.5% (48mmol/mol) at 26 and 34 weeks gestation predicts adverse outcomes in type 1 diabetes. Regular measurements in pregnancy, with expert surveillance when elevated is indicated.

It is now well established that optimising glycemic control in pregnant women with type 1diabetes is associated with improved outcomes (1). However, achieving normoglycemia is not without risks, particularly those associated with maternal hypoglycemia (2).

While there is agreement that poor periconceptual glycemic control increases the risk of congenital malformations (2), much less consensus exists as to the relation of glycemic control later in pregnancy to specific adverse maternal and neonatal outcomes. Possible explanations for this lack of consensus include: the small number of randomised controlled or prospective observational cohort trials; the retrospective design of most studies, comparison of women with good and poor outcomes; minimal standardisation of maternal and neonatal outcome indicators, including composite outcomes; and comparison of glycemic control in different trimesters of pregnancy using different measures of glycemia such as A1C, and meal-related (pre, post, average) measures of glycemic control. In addition, these latter glycemic measures are usually expressed as arbitrary thresholds such as a dichotomy of good or poor control, tertiles of glycemia, or other groupings.

A1C is generally favoured as an estimate of glycemic control as it requires one non-fasting blood sample and represents an objective measurement of glycemic control over the preceding 6-8 weeks. However, the literature would suggest that there is a fall in A1C during pregnancy and that A1C is lower in pregnancy than outside of pregnancy. This requires care with interpretation of results. A systematic review of the relationship between A1C and adverse outcomes (1) reported that an elevated A1C towards the end of the first trimester usually reflects sub-optimal control around the time of conception and in the first trimester, and has been associated with an increased incidence of congenital malformations and miscarriage (3,4). Some studies in type 1 diabetes reporting A1C values in the second or third

trimesters, have demonstrated an association between poor control and an increased risk of stillbirth (4,5), fetal macrosomia or large for gestational age (LGA) (6-10), neonatal intensive care (11) and other adverse outcomes such as preterm delivery(12), pre-eclampsia (13) and composite indicators of adverse outcome (14). Several studies in which women were randomised to either strict or less strict glycemic control were unable to demonstrate an improvement in A1C in the more strictly controlled group (15), however these studies were small and as a consequence no definite conclusions on the degree of glycemic control necessary to impact on outcomes were reached (16). One non-randomised study suggested that very tight control was not necessarily required to obtain satisfactory outcomes, and was associated with more maternal hypoglycemia (17).

Reports which have used self-monitored capillary blood glucose as a measure of glycemic control have tended to compare women with and without adverse outcomes in relation to mean glucose values: either pre-prandial, post-prandial or combined. Karlsson and Kjellmer (18) reported that increased rates of poor pregnancy outcomes were associated with increasing third trimester mean glucose values. Damm et al. (14) demonstrated that more women had poor outcomes when capillary glucose values were outside the normal range. The Diabetes in Early Pregnancy Study (6) showed an association between increasing birth weight and increasing mean post-prandial, but not pre-prandial glycemia, a finding reported elsewhere (19), while other studies suggested a relationship with pre-prandial (20) or mean levels (21). Another approach has been to create arbitrary glycemic thresholds such as good or poor control and some studies have demonstrated higher neonatal morbidity in the poor glycemic control group (22,23). Furthermore, Mello et al. showed that the risk of LGA was increased with poor glycemic control in the second trimester even if glycemic control was good in the third (24). Due to the limitations of self monitoring of glycemic control, Kerssen

et al. (25) used continuous glucose monitoring and in a small study showed a relationship between the median 24 hour glucose level and LGA. Finally, in a randomised controlled trial, Manderson et al. (26) highlighted the relevance of post-prandial glycemia to both maternal and fetal outcomes.

Although these studies have generally demonstrated an association between suboptimal glycemic control and an increased risk of poor pregnancy outcome, they are of limited value in informing clinicians about the optimal glycemic targets required to minimise these risks. In addition, while it is usually possible with treatment to achieve normoglycemia in gestational diabetes and often in type 2 diabetes, this is much more challenging in the pregnant woman with type 1 diabetes and must be constantly balanced against the risks of hypoglycemia. Various guidelines for glycemic control in pregnancy have been proposed. The American Diabetes Association (27) recommends a target A1C below 7% (53 mmol/mol) prior to conception, similar to that recommended in Scotland (28). In the rest of the UK, the National Institute of Clinical Excellence (NICE) guidelines (29) recommend a target A1C of 6.1% or below (43 mmol/mol) prior to conception, if this can be achieved safely. During pregnancy the A1C target in the US is 6.0% (307) with monitoring every 1-3 months. In contrast, UK NICE guidelines advise against routine measurement of A1C in the second and third trimester (29), apparently because of lack of evidence and physiological changes in pregnancy. With regard to glycemic targets, there is fairly close agreement in the US and UK guidelines, with the US advising pre-prandial values 3.3-5.4 mmol/l (60-99mg/dl) and peak post-prandial values between 5.4-7.1 mmol/l (100-129mg/dl) (30), while the UK NICE guidelines recommend pre-prandial capillary glucose target values between 3.5 to 5.9 mmol/l and one hour post-prandial values below 7.8 mmol/l (29). While there is good evidence to

support the statement that poor pregnancy outcomes are more likely to be associated with sub-optimal glycemic control during pregnancy, there is actually minimal data to inform clinical targets for either A1C or glucose and so to date, guidelines have been based mainly on expert opinion.

Given this background, the aim of this study was to assess the relationship between glycemic control, as assessed by both A1C and capillary blood glucose profiles in the second and third trimesters of pregnancy, and maternal and neonatal outcomes, in a large prospective cohort of women with type 1 diabetes.

Methods

The study population comprised 762 women with type 1 diabetes recruited from 25 joint antenatal-metabolic clinics across Northern Ireland, North West England and Scotland between April 2003 and June 2008 into the Diabetes and Pre-eclampsia Intervention Trial (DAPIT). DAPIT was a multi-centre randomised, placebo-controlled trial of Vitamin C and E supplementation to prevent pre-eclampsia in pregnant women with type 1 diabetes. As no effect of antioxidant vitamins on the development of pre-eclampsia was demonstrated, the active treatment and placebo groups were combined for analysis (31).

Details of the methodology have been described previously (13, 31). In brief, women with type 1 diabetes were recruited between 8-22 weeks gestation and randomised to vitamin C and E supplementation or matched placebo. 762 women were recruited, with 749 women progressing to at least 20 weeks' gestational age. The 725 women who subsequently delivered an infant without a major malformation were included in this analysis. At the first antenatal-metabolic clinic visit, details including ethnicity, parity, years of education, social class and smoking habits were recorded and BMI and A1C measured. Subsequently women were reviewed at 26 (±2) weeks' gestation and at 34 (±2) weeks' gestation when venous blood samples were obtained for measurement of A1C. The samples were stored at -70ºC for transportation to the Nutrition and Metabolism Laboratories, Queen's University Belfast and batch assayed at the end of the study. A1C (Diazyme Laboratories, Poway, CA) was measured by spectrophotometry using an automated ILab600 biochemical analyser. As a National Glycohaemoglobin Standardization Program and International Federation for Clinical Chemistry certified method, the values reported were aligned with the Diabetes Control and Complications Trial system, with intra- and interassay coefficients of variation

<2%. A1C results were arbitrarily grouped by 0.5% intervals from <6.0 (42mmol/mol) to ≥7.5% (59mmol/mol), with <6.0% (42mmol/mol) taken as the reference group. All women were requested to measure their capillary blood glucose on a standardised meter 8 times a day (pre and 1h post meals and at bedtime) and to record the values on the day prior to the 26 and 34 week study visit. The mean of the fasting/pre-prandial values and the mean of the post-prandial values were analysed in relation to 1 mmol/l increments; for pre-prandial the range was from < 5.0 to ≥8.0 mmol/l and for post-prandial <6.0 to ≥9.0mmol/l. The lowest group in both cases was taken as the reference.

Maternal and neonatal outcomes were as previously specified (31), but only a selection has been analysed here. Pre-eclampsia, was defined as gestational hypertension and proteinuria in accordance with the International Society for the Study of Hypertension in Pregnancy (32). Birthweight centiles were calculated using customised birthweight charts (33) and those >90th centile classified as large for gestational age (LGA). Admission to a neonatal unit was defined as either high dependency or intensive care (levels 2 and 3), with these levels of care being rigorously defined. Neonatal hypoglycemia was defined by the need for an intravenous glucose infusion and neonatal hyperbilirubinaemia by the need for phototherapy. In addition caesarean delivery and gestation at delivery were also considered. As serious adverse outcomes are rare, a composite outcome variable composed of several individual adverse endpoints was also included. Unfortunately no such standardised outcome exists in the literature and neither was one specified in the DAPIT study. The composite outcome employed here was adapted from that used in the ACHOIS study (34) (namely perinatal death, shoulder dystocia, fractures or nerve palsy), with the addition of admission to the neonatal intensive care unit for level 2 or 3 care.

The West Midlands Multicentre Research Ethics Committee provided ethical approval (MREC 02/7/016). The study was registered as an International Standard Randomised Controlled Trials, ISRCTN 27214045.

Statistical analysis

Comparisons of outcomes in groups defined by A1C levels or by averaged capillary blood glucose levels at 26 or 34 weeks were performed using the χ^2 test for trend in contingency tables. Logistic regression was used to estimate the odds of outcomes in each group relative to the group with lowest A1C or averaged glucose values, with results expressed as odds ratios with 95% confidence intervals. This was done both before and after adjustment for potentially confounding variables (age, BMI, ethnicity, diabetes duration, parity, current smoking, years of education, social class, plasma ascorbate and serum α-tocopherol at randomisation, microalbuminuria before pregnancy, vitamin treatment group and center). All statistical analyses were performed using SPSS software, version 20 (IBM Corp., Armonk, NY, USA).

Results

Maternal characteristics and glycemic control are shown in Table 1. Further characteristics have previously been described in detail (31).

A1C results were available for 576 (79%) and 505 (70%) participants at 26 and 34 weeks' gestation, respectively. Maternal and neonatal outcomes by A1C groups are described in Tables 2 and 3, showing both the unadjusted and adjusted rates allowing for specific confounders. With higher values of A1C there were increasing risks of pre-eclampsia, pre-term delivery, LGA, neonatal hypoglycemia requiring a glucose infusion, hyperbilirubinaemia requiring phototherapy and a composite adverse outcome. The less common outcomes of birthweight <10th centile (rate 3%) and Apgar score at 5 minutes < 7 (rate 2%) were also investigated, and no significant relationship found. Ethnicity had no effects on outcomes. Allowing for A1C values in the first or early second trimester of pregnancy had a slight modifying effect on the degree of significance of some of the outcomes, but the trends remained (Supplemental Tables S1and S2)).

The A1C measurements at 26 and 34 weeks were strongly correlated (r=0.8) resulting in the associations between A1C at 34 weeks and adverse outcomes, adjusted for A1C at 26 weeks, being weakened and in many cases non-significant; a similar finding occurred with analysis of A1C at 26 weeks adjusting for A1C at 34 weeks (data not shown). However, the 41 women with A1C ≥6.5% (48mmol/mol) in the second trimester, but < 6.5% (48mmol/mol) in the third, had significantly fewer LGA babies (p=0.033) with a trend towards fewer adverse composite outcomes (p=0.065) and cases of preterm delivery (p=0.064) compared with those women whose A1c remained ≥6.5% (48mmol/mol) in both trimesters (n=191). However, the number of subjects was small and the data need to be interpreted with caution.

Comparison of the women with and without A1C measurements at 26 and 34 weeks showed some differences with regard to maternal age in that the women with missing data were about 1 year younger (although of similar BMI, diabetes duration and total daily dose of insulin), and they were also recruited about 1 week later. In addition at 34 weeks there were significantly more nulliparous women with missing data, but there was no difference at 26 weeks.

Average pre-/post-prandial capillary blood glucose results were available for 610 (84%)/484 (67%) and 546 (75%)/447 (62%) participants at 26 and 34 weeks', respectively. The maternal and neonatal outcomes according to capillary blood glucose categories are shown in Table 4 and Supplemental Tables S3-5. Significant linear trends were demonstrated for LGA with pre-prandial glycemia at both 26 ($p<0.001$) and 34 ($p<0.05$) weeks' gestation. For post-prandial glycemia significant trends for LGA were again demonstrated at 26 ($p<0.03$) and 34 ($p<0.02$) weeks' gestation. No other significant trends were demonstrated for post-prandial glycemia (Supplemental Tables S 4, 5). However, increasing pre-prandial glycemia was also associated with significantly increasing rates of preterm delivery at both 26 weeks' (OR 2.0, 95% CI 1.1-3.7 when glucose 7.0-7.9mmol/l) and at 34 weeks' (OR 2.4, 95% CI 1.2-5.0 when glucose≥8.0mmol/l) (Table 4 and Supplemental Table 3). Other significant associations with pre-prandial glycemia at 34 weeks were also demonstrated (Table 4).

Conclusions

This large, prospective study of women with type 1 diabetes has demonstrated a relationship between increasing A1C categories during the second and third trimesters of pregnancy and a series of relevant, rigorously defined adverse maternal and neonatal outcomes including a composite neonatal outcome. Unlike previous data, this study gives a much clearer picture of the A1C and capillary glucose targets which should be aimed for to minimise the risk of adverse outcomes.

While a randomised controlled trial is the gold standard for looking at the association between varying degrees of glycemic control and adverse pregnancy outcomes such a design is impractical and most likely unethical. Previous studies have been too small (16, 17) to examine the main outcomes included in the current study, and thus only a large prospective observational study would appear feasible. Although the primary outcome of the DAPIT trial was pre-eclampsia, prospective documentation of other pre-specified outcomes, together with A1C measurements in each trimester, permitted utilisation of this valuable cohort of subjects with type 1 diabetes to examine the important question of the relationship between glycemic control in later pregnancy and maternal and neonatal outcomes. However, given the rarity of outcomes such as perinatal death and birth trauma, prior to data analysis, we considered it necessary to derive a composite adverse neonatal outcome which we defined as that used in the ACHOIS study (34), combined with need for admission to level 2 or level 3 neonatal intensive care as defined in the DAPIT trial. Prior to data analysis, A1C and blood glucose categories were also agreed.

The association of increasing A1C in early pregnancy and the risk of miscarriage and congenital anomalies is well established (35). However, while a number of studies have

shown an association between deteriorating glycemic control and an increased risk of adverse outcomes, few have data relating specific A1C target values later in pregnancy with adverse outcomes, and some national guidelines question the clinical utility of A1C measurements outside the first trimester. Indeed in the UK, the current NICE guidelines suggest that A1C should not be measured in the second and third trimester (29), presumably on the basis of lack of evidence to support its measurement and concern regarding interpretation of the result given the physiological fall in A1C during pregnancy. The present study has clearly demonstrated an increased risk of adverse outcomes in later pregnancy with increasing A1C values. Tennant and colleagues (5) showed an increasing rate of stillbirths and neonatal deaths with increasing maternal A1C. However, our data has the advantage of being collected prospectively and includes the examination of a wide range of maternal and neonatal outcomes by specific target ranges of A1C and pre- and post-prandial capillary blood glucose measurements. In addition, unlike most previous studies, pregnancies complicated by a major congenital anomaly were excluded to focus on adverse outcomes associated with glycemic control in the second and third trimester.

We found a striking linear relationship between A1C categories and the composite adverse neonatal outcome, and even for A1C 6.5-6.9% (48-52mmol/mol) the risk was significantly increased at 26 and 34 weeks' gestation. Macrosomia, is a commonly reported outcome which has previously been associated with increasing A1C (6-10), and we have shown a clear association with the strict definition of birthweight >90thcentile (LGA), using customised birthweight charts. There was a linear trend with increasing A1C, and a significant increase in LGA even for the A1C category 6.0-6.4% (42-47mmol/mol) both at 26 and 34 weeks' gestation. Neonatal hypoglycemia is an indicator of maternal antenatal glycemic control, but is difficult to standardise because of differing definitions and sampling times. Accordingly, we utilised a more robust measure, namely treatment with an intravenous glucose infusion,

and found a linear increase in neonatal hypoglycemia with increasing A1C, a significant increase being present for A1C between 6.5-6.9% (48-52mmol/mol). Similar relationships were demonstrated with preterm delivery. Hyperbilirubinemia, a recognised neonatal complication of the baby born to a mother with diabetes, and not reported in other studies, also showed a linear trend with increasing maternal A1C, although significance was not apparent until A1C ≥ 7.0% (53mmol/mol). A previous analysis of the DAPIT cohort, showed an increasing risk of pre-eclampsia with increasing A1C (13) and further analysis here showed a significant increased risk with A1C ≥ 6.5% (48mmol/mol) at 26 and 34 weeks' gestation. Furthermore, we found that the relationships between the adverse outcomes and A1C values in the second and third trimesters persisted even after controlling for A1C in the first or early second trimester. Increasing A1C values had no apparent impact on cesarean section rates, perhaps not surprising given the many factors which contribute to this outcome.

Our study indicates the clinical utility of regular A1C measurements throughout pregnancy in predicting whether a woman is at an increased risk of an adverse outcome. While measurement of A1C does not necessarily motivate behaviour change, our data does suggest that A1C values ≥ 6.5% (48mmol/mol), identify women at increased risk of adverse outcomes. This was shown particularly at 26 weeks, but less so at 34 weeks. Clinically, these findings would support regular measurement of A1C every 1-3 months throughout pregnancy as advised in the US (30).). Our data shows that for some outcomes such as LGA, the risk is already present when the A1C is ≥ 6.0% (42mmol/mol), but such values may not be achievable in routine practice because of hypoglycaemia and targets must be realistic and individualised. However, the data indicate that those women with A1C values in the second trimester ≥6.5% (48mmol/mol) need to be counselled about the increased risk of adverse

outcomes. The risks of stillbirth are present throughout the third trimester (36) and if A1C is ≥ 6.5% (48mmol/mol), such women require intensive supervision by experienced clinicians. This may include more frequent clinic visits and in some women even a short period of hospitalisation. We also suggest that ultrasound scans should be performed more frequently than the 4 weekly interval, as currently recommended by NICE (29) with careful review of the results, as poor data interpretation was found to be associated with an increased risk of adverse outcomes (37). In the US, more detailed fetal assessment including biophysical profile testing, cardiotocography and Doppler umbilical artery velocimetry have been advised for most patients from about 32 weeks (38), although the benefits of such detailed assessments remain unclear.

On a day to day basis, however, it is the results of pre- and post-prandial monitoring, rather than monthly A1C results, which provide immediate feedback on glucose excursions and guide insulin adjustment. This study has allowed investigation of the effect of varying degrees of glycemia in the second and third trimester on specific maternal and neonatal outcomes. Self reported measurements do have limitations and in this study pertained to one particular day in the second and third trimester. While a significant number of women had missing data, and there were some differences in the characteristics of women with and without readings, it seems unlikely that these differences would have significant clinical implications. We are unaware of other studies of this size which have considered multiple maternal and neonatal outcomes in relation to such an extensive dataset of glucose measures and it is probable that none will be forthcoming until results from large studies using continuous glucose monitoring become available, although smaller studies have revealed an association with LGA babies (25). While the relationship between glucose data and adverse outcomes does not show such a clear trend as with A1C, there was evidence of an increased linear risk of LGA with both pre- and post-prandial glucose concentrations. This is in accord

with previous studies which have shown relationships with pre-prandial glycemia (20), post-prandial glycemia (7, 19) and mean glucose levels (21, 24, 25). In the present study, a number of neonatal adverse outcomes were significantly related to pre-prandial rather than post-prandial values particularly at the 34 weeks' gestation time point. These included the composite adverse neonatal outcome, neonatal hypoglycemia requiring a glucose infusion, hyperbilirubinaemia requiring phototherapy and preterm delivery. We are not aware of other studies which have reported an association between these outcomes and worsening pre-prandial glycemic control. These results suggest that glycemic control during fasting and pre-prandial periods may be more relevant to adverse outcomes than the shorter post-prandial periods of hyperglycemia.

In summary, the current study has shown a continuous relationship between multiple maternal and neonatal adverse outcomes and increasing A1C values in the second and third trimester of pregnancy in women with type 1 diabetes. These adverse outcomes were significantly associated with A1C of ≥6.5% (48mmol/mol) and LGA with an A1C ≥6.0% (42mmol/mol). We feel that women should be advised to aim for target values of <6.5% (48mmol/mol) and ideally <6.0% (42mmol/mol) if this is possible without excessive hypoglycemia. For women in whom this goal is not achieved, additional surveillance by experienced clinicians is indicated. While capillary blood glucose data were generally concordant with the A1C results, it was not possible to define a clear target range, although third trimester pre-prandial glucose values between 6.0- 6.9mmol/l were associated with an increased risk of an adverse composite neonatal outcome. This is in agreement with current ADA and NICE guidelines which recommend pre-prandial glucose values of <5.5 and

<6.0mmol/l, respectively (27,29). Finally, our data suggest that current UK NICE guidelines, with regard to the usefulness of A1C in later pregnancy, need to be reviewed.

M.J.A.M researched the data and wrote, reviewed and edited the manuscript. V.A.H, C.C.P, J.D.W, D.W.M.P, I.S.Y. and D.R.M researched the data, contributed to the discussion and reviews and edited the manuscript.

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Dr Michael Maresh is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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No potential conflicts of interest relevant to this article were reported.

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Age (years) mean (SD)	29.6 (5.6)
Body Mass Index (kg m^{-2}) mean (SD) *	27.4 (4.7)
Diabetes duration (yr) mean (SD)	14.5 (8.2)
Primiparous n (%)	361 (49.8%)
Smoker n (%)	139 (19.2%)
Social class – head of household in professional or managerial/ technical occupation n (%) †	297 (46.0%)
Non-white ethnicity n (%)	26 (3.6%)
Education (yr) mean(SD)	14.0 (2.8)
A1C (%: mmol/mol) mean (SD) ‡	
First antenatal visit	7.8 (1.4): 62 (15)
26 weeks gestation	6.7 (0.8): 50 (9)
34 weeks gestation	6.6 (0.7): 48 (7)
Mean fasting/pre-prandial capillary glucose (mmol/l) mean (SD) §	
26 weeks gestation	6.4 (1.8)
34 weeks gestation	6.0 (1.7)
Mean 1 hour post-prandial capillary glucose (mmol/l) mean (SD) ‖	
26 weeks gestation	7.5 (2.4)
34 weeks gestation	7.2 (2.3)

*Based on n=708 results

† Based on n=646 results

‡ Based on n= 698/576/505 results at first antenatal visit/26 weeks gestation/34 weeks gestation

§ Based on n= 610/546 results at 26weeks gestation/34 weeks gestation

‖ Based on n= 484/447 results at 26weeks gestation/34 weeks gestation

Table 1: Maternal characteristics and glycemic control in 725 participants

		A1C at 26 weeks					
		<6.0 % (<42 mmol/mol) n = 101	6.0-6.4% (42-47 mmol/mol) n = 176	6.5-6.9% (48-52 mmol/mol) n = 128	7.0-7.4% (53-58 mmol/mol) n = 98	7.5+ % (59+ mmol/mol) n = 73	P value for trend
Pre-eclampsia	Number (%)	8/101 (8%)	23/176 (13%)	29/128 (23%)	24/98 (24%)	17/73 (23%)	
	OR (95%CI)	1.0 reference	1.7 (0.8, 4.1)	3.4‡ (1.5, 7.8)	3.8‡ (1.6, 8.9)	3.5‡ (1.4, 8.7)	<0.001
	OR (95%CI) *	1.0 reference	2.0 (0.8, 4.9)	4.3‡ (1.7,10.8)	4.6‡ (1.8,12.0)	5.1‡ (1.9,14.1)	<0.001
Large for gestational age (>90th centile)	Number (%)	36/99 (36%)	88/175 (50%)	73/128 (57%)	60/98 (61%)	46/73 (63%)	
	OR (95%CI)	1.0 reference	1.8† (1.1, 2.9)	2.3‡ (1.4, 4.0)	2.8§ (1.6, 4.9)	3.0§ (1.6, 5.6)	<0.001
	OR (95%CI) *	1.0 reference	1.7† (1.0, 3.0)	2.5‡ (1.4, 4.5)	3.2§ (1.7, 6.1)	3.7§ (1.8, 7.5)	<0.001
Cesarean section delivery	Number (%)	67/101 (66%)	125/176 (71%)	85/128 (66%)	76/98 (78%)	46/73 (63%)	
	OR (95%CI)	1.0 reference	1.2 (0.7, 2.1)	1.0 (0.6, 1.7)	1.8 (0.9, 3.3)	0.9 (0.5, 1.6)	0.90
	OR (95%CI) *	1.0 reference	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)	2.0 (1.0, 3.9)	1.0 (0.5, 1.9)	0.48
Neonatal hypoglycemia requiring glucose infusion	Number (%)	20/99 (20%)	42/170 (25%)	49/124 (40%)	39/95 (41%)	30/70 (43%)	
	OR (95%CI)	1.0 reference	1.3 (0.7, 2.4)	2.6‡ (1.4, 4.7)	2.8‡ (1.5, 5.2)	3.0‡ (1.5, 5.9)	<0.001
	OR (95%CI) *	1.0 reference	1.5 (0.8, 2.9)	2.9‡ (1.5, 5.6)	3.5§ (1.7, 7.2)	3.8§ (1.7, 8.2)	<0.001
Hyperbilirubinemia requiring phototherapy	Number (%)	13/99 (13%)	25/173 (14%)	26/127 (20%)	28/96 (29%)	20/71 (28%)	
	OR (95%CI)	1.0 reference	1.1 (0.5,2.3)	1.7 (0.8, 3.5)	2.7‡ (1.3, 5.7)	2.6† (1.2, 5.7)	<0.001
	OR (95%CI) *	1.0 reference	1.4 (0.6, 2.9)	2.1 (0.9, 4.5)	3.7‡ (1.7, 8.3)	3.8‡ (1.6, 8.9)	<0.001
Delivery before 37 weeks	Number (%)	21/101 (21%)	51/176 (29%)	48/128 (38%)	50/98 (51%)	33/73 (45%)	
	OR (95%CI)	1.0 reference	1.6 (0.9, 2.8)	2.3‡ (1.3, 4.2)	4.0§ (2.1, 7.4)	3.1§ (1.6, 6.1)	<0.001
	OR (95%CI) *	1.0 reference	1.6 (0.8, 2.9)	2.5‡ (1.3, 4.8)	5.1§ (2.6,10.2)	3.8§ (1.8, 8.0)	<0.001
Composite adverse neonatal outcome	Number (%)	8/101 (8%)	21/176 (12%)	25/128 (20%)	27/98 (28%)	16/73 (22%)	
	OR (95%CI)	1.0 reference	1.6 (0.7, 3.7)	2.8† (1.2, 6.6)	4.4§ (1.9,10.3)	3.3† (1.3, 8.1)	<0.001
	OR (95%CI) *	1.0 reference	1.6 (0.7, 4.1)	3.2‡ (1.3, 8.0)	6.7§ (2.6,17.0)	4.4‡ (1.6,12.3)	<0.001

† P<0.05, ‡ P<0.01, § P<0.001

* Adjusted for age, body mass index, years of education, social class, ethnicity, parity, current smoking, duration of diabetes, microalbuminuria before pregnancy, vitamin treatment group and center.

Table 2 Adverse pregnancy outcomes by A1C category at 26 weeks gestation

		A1C at 34 weeks										
		<6.0 % (<42 mmol/mol) n = 98		6.0-6.4% (42-47 mmol/mol) n = 165		6.5-6.9% (48-52 mmol/mol) n = 136		7.0-7.4% (53-58 mmol/mol) n = 66		7.5+ % (59+ mmol/mol) n = 40		P value for trend
Pre-eclampsia	Number (%)	8/98	(8%)	23/165	(14%)	19/136	(14%)	12/66	(18%)	11/40	(28%)	
	OR (95%CI)	1.0	reference	1.8	(0.8, 4.3)	1.8	(0.8, 4.4)	2.5	(1.0, 6.5)	4.4‡	(1.6,11.6)	0.005
	OR (95%CI)*	1.0	reference	2.4	(0.9, 6.3)	3.0†	(1.1, 7.9)	5.3‡	(1.7,16.9)	6.8‡	(2.1,22.8)	<0.001
Large for gestational age (>90th centile)	Number (%)	33/98	(34%)	77/165	(47%)	91/136	(67%)	44/65	(68%)	21/40	(53%)	
	OR (95%CI)	1.0	reference	1.7†	(1.0, 2.9)	4.0§	(2.3, 6.9)	4.1§	(2.1, 8.0)	2.2†	(1.0, 4.6)	<0.001
	OR (95%CI)*	1.0	reference	1.9†	(1.1, 3.3)	4.6§	(2.5, 8.5)	5.6§	(2.6, 12.0)	2.9†	(1.3, 6.7)	<0.001
Cesarean section delivery	Number (%)	62/98	(63%)	107/165	(65%)	99/136	(73%)	51/66	(77%)	23/40	(58%)	
	OR (95%CI)	1.0	reference	1.1	(0.6, 1.8)	1.6	(0.9, 2.7)	2.0	(1.0, 4.0)	0.8	(0.4, 1.8)	0.35
	OR (95%CI)*	1.0	reference	0.9	(0.5, 1.7)	1.7	(0.9, 3.2)	2.4†	(1.1, 5.4)	0.7	(0.3, 1.7)	0.26
Neonatal hypoglycemia requiring glucose infusion	Number (%)	18/97	(19%)	39/158	(25%)	45/133	(34%)	25/64	(39%)	17/38	(45%)	
	OR (95%CI)	1.0	reference	1.4	(0.8, 2.7)	2.2†	(1.2, 4.2)	2.8‡	(1.4, 5.8)	3.6‡	(1.6, 8.1)	<0.001
	OR (95%CI)*	1.0	reference	1.7	(0.9, 3.5)	2.8‡	(1.4, 5.8)	4.1‡	(1.8, 9.8)	4.8‡	(1.9,12.4)	<0.001
Hyperbilirubinemia requiring phototherapy	Number (%)	11/98	(11%)	24/162	(15%)	17/134	(13%)	16/65	(25%)	13/39	(33%)	
	OR (95%CI)	1.0	reference	1.4	(0.6, 2.9)	1.1	(0.5, 2.6)	2.6†	(1.1, 6.0)	4.0‡	(1.6, 9.9)	0.002
	OR (95%CI)*	1.0	reference	1.7	(0.7, 3.9)	1.3	(0.5, 3.3)	3.0†	(1.1, 7.9)	5.4‡	(1.9,15.5)	0.002
Delivery before 37 weeks	Number (%)	17/98	(17%)	38/165	(23%)	48/136	(35%)	27/66	(41%)	16/40	(40%)	
	OR (95%CI)	1.0	reference	1.4	(0.8, 2.7)	2.6‡	(1.4, 4.9)	3.3‡	(1.6, 6.8)	3.2‡	(1.4, 7.2)	<0.001
	OR (95%CI*	1.0	reference	1.4	(0.7, 2.9)	3.0‡	(1.5, 6.1)	4.2§	(1.8, 9.7)	4.0‡	(1.6,10.4)	<0.001
Composite adverse neonatal outcome	Number (%)	7/98	(7%)	14/165	(8%)	20/136	(15%)	13/66	(20%)	12/40	(30%)	
	OR (95%CI)	1.0	reference	1.2	(0.5, 3.1)	2.2	(0.9, 5.5)	3.2‡	(1.2, 8.5)	5.6‡	(2.0,15.5)	<0.001
	OR (95%CI)*	1.0	reference	1.4	(0.5, 4.0)	2.7	(1.0, 7.5)	5.5‡	(1.7,17.6)	9.4§	(2.8,31.2)	<0.001

† P<0.05, ‡P<0.01, § P<0.001

* Adjusted for age, body mass index, years of education, social class, ethnicity, parity, current smoking, duration of diabetes, microalbuminuria before pregnancy, vitamin treatment group and center.

Table 3 Adverse pregnancy outcomes by A1C category at 34 weeks gestation

		Pre-prandial average glucose at 34 weeks					
		<5.0 mmol/l	5.0-5.9 mmol/l	6.0-6.9 mmol/l	7.0-7.9 mmol/l	8.0+ mmol/l	P value
		n = 158	n = 176	n = 90	n = 64	n = 58	for trend
Pre-eclampsia	Number (%)	20/158 (13%)	25/176 (14%)	15/90 (17%)	11/64 (17%)	9/58 (15.5%)	
	OR (95%CI)	1.0 reference	1.1 (0.6, 2.1)	1.4 (0.7, 2.9)	1.4 (0.6, 3.2)	1.3 (0.5, 3.0)	0.37
	OR (95%CI)*	1.0 reference	1.0 (0.5, 2.0)	1.2 (0.5, 2.6)	1.3 (0.5, 3.3)	1.3 (0.5, 3.3)	0.44
Large for gestational age	Number (%)	74/158 (47%)	96/175 (55%)	49/90 (54%)	33/64 (52%)	37/58 (64%)	
(>90th centile)	OR (95%CI)	1.0 reference	1.4 (0.9, 2.1)	1.4 (0.8, 2.3)	1.2 (0.7, 2.2)	2.0† (1.1, 3.7)	0.07
	OR (95%CI)*	1.0 reference	1.4 (0.9, 2.2)	1.4 (0.8, 2.4)	1.1 (0.6, 2.1)	2.5‡ (1.2, 5.0)	0.05
Cesarean section delivery	Number (%)	103/158 (65%)	118/176 (67%)	61/90 (68%)	42/64 (66%)	45/58 (78%)	
	OR (95%CI)	1.0 reference	1.1 (0.7, 1.7)	1.1 (0.6, 1.9)	1.0 (0.6, 1.9)	1.8 (0.9, 3.7)	0.19
	OR (95%CI)*	1.0 reference	0.9 (0.6, 1.5)	1.0 (0.6, 1.9)	0.9 (0.5, 1.8)	1.5 (0.7, 3.1)	0.45
Neonatal hypoglycaemia	Number (%)	33//155 (21%)	47/173 (27%)	26/86 (30%)	22/63 (35%)	20/55 (36%)	
requiring glucose infusion	OR (95%CI)	1.0 reference	1.4 (0.8, 2.3)	1.6 (0.9, 2.9)	2.0† (1.0, 3.8)	2.1† (1.9, 4.1)	0.009
	OR (95%CI)*	1.0 reference	1.4 (0.8, 2.5)	1.7 (0.9, 3.4)	1.9 (0.9, 3.9)	1.9 (0.9, 4.0)	0.04
Hyperbilirubinaemia	Number (%)	14/157 (9%)	30/175 (17%)	14/87 (16%)	12/64 (19%)	11/57 (19%)	
requiring phototherapy	OR (95%CI)	1.0 reference	2.1† (1.1, 4.2)	2.0 (0.9, 4.3)	2.4† (1.0, 5.4)	2.4† (1.0, 5.8)	0.04
	OR (95%CI)*	1.0 reference	2.1† (1.0, 4.3)	2.0 (0.9, 4.7)	2.8† (1.1, 6.9)	2.9† (1.1, 7.4)	0.02
Delivery before 37 weeks	Number (%)	31/158 (20%)	55/176 (31%)	25/90 (28%)	19/64 (30%)	22/58 (38%)	
	OR (95%CI)	1.0 reference	1.9† (1.1, 3.1)	1.6 (0.9, 2.9)	1.7 (0.9, 3.4)	2.5‡ (1.3, 4.8)	0.02
	OR (95%CI)*	1.0 reference	1.6 (0.9, 2.7)	1.5 (0.8, 2.9)	1.6 (0.8, 3.2)	2.4† (1.2, 5.0)	0.03
Composite adverse neonatal	Number (%)	11/158 (7%)	23/176 (13%)	15/90 (17%)	9/64 (14%)	13/58 (22%)	
outcome	OR (95%CI)	1.0 reference	2.0 (0.9, 4.3)	2.7† (1.2, 6.1)	2.2 (0.9, 5.6)	3.9‡ (1.6, 9.2)	0.003
	OR (95%CI)*	1.0 reference	1.9 (0.8, 4.2)	3.3‡ (1.3, 8.0)	2.6 (1.0, 7.2)	5.6§ (2.1,14.5)	<0.001

† P<0.05, ‡ P<0.01, § P<0.001

*Adjusted for age, body mass index, years of education, social class, ethnicity, parity, current smoking, duration of diabetes, microalbuminuria before pregnancy, vitamin treatment group and center.

Table 4 Adverse pregnancy outcomes by average pre-prandial glucose category at 34 weeks gestation